Information Disclosure Statement

The Examiner states that an Information Disclosure Statement was filed on May 24, 2001, but that this paper cannot be located. The Examiner invited Applicant to replace the IDS and that the replacement would be entered and treated as if filed on May 24, 2001. Accordingly, Applicant submits herewith a copy of the IDS filed on May 24, 2001.

Claim Objections

Claim 10 is objected to because in line 1, "conformation" should read "conformational." Applicant has amended claim 10 to include the word "conformational." Withdrawal of this objection is requested.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 4-7, 25-27, 30, 93, and 99 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection has several aspects, which are addressed individually below.

The Examiner states that claims 4-7 are indefinite because claim 4 recites "the dissociation constant (KD)..."while claims 5-7 recite the binding constant (Kd)..." Claims 5-7 have been amended to recite "dissociation constant" so that they are the same as claim 4. In light of this amendment, withdrawal of this aspect of the rejection is requested.

The Examiner states that claims 25, 26, and 27 are indefinite because each depends from canceled claim 2. The recitation of claim 2 in dependent claims 25, 26, and 27 has been deleted. Withdrawal of this aspect of the rejection is respectfully requested.

The Examiner states that claims 30 and 99 are indefinite in reciting "treating a patient infected with HCV" comprising "providing a patient infected with HCV or susceptible to HCV infection." Specifically, the Examiner states that it is not clear whether the method is intended to be a method for treating or a method for preventing HCV infection. Claims 30 and 99 have been amended to clearly recite that the method is a method for treating or preventing HCV infection in a patient. In light of this amendment, withdrawal of this aspect of the rejection is requested.

The Examiner states that claim 32 is indefinite in reciting "the step of administering the antibody comprises administering more than one different antibody. The Examiner further states that it is not clear whether the additional antibody or antibodies must also be an antibody within the scope of claim 1, or whether it or they can be any different antibody. Claim 32 has been amended to recite "the step of administering the antibody comprises administering more than one different antibody directed to a conformational epitope of a protein of Hepatitis C virus." The phrase "directed to a conformational epitope of a protein of Hepatitis C virus" is from claim 1 and comprises any antibody within the scope of claim 1. In light of this amendment, withdrawal of this aspect of the rejection is requested.

The Examiner states that claim 66 is indefinite because the basis for identifying a patient as a candidate for administration of a treatment is not specified, nor is the nature of the treatment for which the patient is a candidate specified or made clear. Claim 66 has been canceled. Withdrawal of this aspect of the rejection is requested.

The Examiner states that claim 70 is indefinite in reciting "wherein the step of administering comprises" without antecedent in claim 66, which only recites, "providing," "measuring," and "identifying." Claim 70 has been amended to depend from claim 67, which does recite the step of administering, providing the proper antecedent basis for claim 70. In light of this amendment, withdrawal of this aspect of the rejection is requested.

The Examiner states that claim 93 is confusing in reciting " the combination results in.", since it would seem that binding of the combination, and not merely the presence of the combination, is required. The Examiner further states that claim 93 is confusing because it appears to encompass an embodiment in which two or more antibodies will result in increased binding to that same epitope, yet it requires that the combination of antibodies will result in increased binding to that same epitope.

Claim 93 has been amended to recite the combination of claim 92, wherein the combination shows increased total binding E2 protein of Hepatitis C virus compared to either antibody individually. This amendment clarifies that it is the presence of binding of all antibodies in the combination of the two or more antibodies that causes the increased total binding to E2. In light of the above, withdrawal of this aspect of the rejection is requested.

The Examiner states that claim 94 is indefinite in reciting, "the increased binding...is greater than 100% relative to the binding of a single antibody." The Examiner further states that it is not clear how the binding is to be measured, and it is not clear whether "greater than 100%" encompasses any amount of increase at all, such as 100.1%, e.g., of the binding of the single antibody, or whether it requires that the binding increase, by whatever measure, be at least two-fold, i.e., a greater than 100% increase, compared to the binding of a single antibody.

Claim 94 has been canceled. In light of this amendment, withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 4-7 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner points to the dissociation constants provided in claims 4-7. The Examiner states that while the original claim may be taken to provide written description, the specification does not appear to teach or describe the production and/or selection of antibodies to conformational epitopes of hepatitis C virus with particular values for binding constants, or characterized according to their binding constants for their epitopes. In response, Applicants have amended the specification to recite the dissociation constants provided in claims 4-7 in the Summary of the Invention. No new matter has been added to the application because claims 4-7 were present in the originally filed application. In light of this amendment, withdrawal of this aspect of the rejection is requested.

Claims 12, 13, 95, 96, and 97 were rejected under 35 U.S.C., first paragraph, for lack or enablement. The Examiner states that the antibodies designated CBH-2, -4D, -4B, -4G, -5, -7, -8C, -8E, -9, -11, and –17 are required in order to practice the invention as claimed since each is specifically recited in one or more of claim 12, 13, 95, 96, and 97. The Examiner states that a biological deposit is required as set forth in 37 CFR 1.801-1.809.

A biological deposit of hybridoma cell lines has been submitted to the ATCC under the Budapest Treaty. Mouse/human heteromyeloma cell lines producing human monoclonal

antibodies designated CBH-2 (ATCC PTA-4465), CBH-4B (ATCC PTA-4466), CBH-4D (ATCC PTA-4467), CBH-4G (ATCC PTA-4468), CBH-5 (ATCC PTA-4469), CBH-7 (ATCC PTA-70), CBH-8C (ATCC PTA-4471), CBH-11 (ATCC PTA-4472), and CBH-17 (ATCC PTA-4473) were deposited and assigned the ATTC numbers indicated. Confirmation of the deposit is attached as Exhibit A. All hybridomas that were not deposited with the ATCC have been deleted from the claims. In light of the submission of the biological deposit and amendment of the claims, withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph is requested. Concerning foreign rights, however, we are not conceding that cancellation of these antibodies from the claims is required.

In order to comply with the biological deposit requirements, Applicant also submits a Statement (submitted herewith entitled Statement Under 37 CFR 1.804(b)) from a person, Dr. Steven Foung, who is in a position to corroborate the fact, stating that the biological material, which is deposited, is a biological material specifically identified in the application as filed.

In accordance with ATCC policies and procedures 1) access to the deposit will be available during pendency of the application to one determined by the Commissioner to be entitled thereto under § 1.14 and 35 U.S.C. 122; and 2) subject to paragraph (b) of 37 CFR 1.808, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent (See Statement Under 37 CFR 1.808(a) and (b) submitted herewith).

Applicant further submits an amendment to the specification adding the accession number for the deposit, the date of the deposit, the name and address of the depository, and a

description of the deposited biological material sufficient to specifically identify it, permit examination, and verify that the deposited biological material is in fact disclosed.

Claims 29, 30-32, 66, 67, 70, and 98-100 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that the claims are not limited to administration of CBH-2 and CBH-7. The Examiner further argues that, even so, there is no indication that administration of such antibodies would have any beneficial effect. The Examiner states that the specification does not provide a basis for correlating results of the *in vitro* assay with obtaining a beneficial result, either protective or therapeutic, in a patient to whom the antibodies as claimed are administered. Applicant disagrees.

It has been shown by Piero Pileri *et al.* (Science, (October 30, 1998) 282:938-941 (Exhibit B)) that the *in vitro* neutralization of binding (NOB) assay can be a reliable measure of *in vivo* neutralization activity of antibodies. Pileri *et al.* correlated the ability of antibodies to neutralize binging in an NOB assay with their ability to neutralize infection *in vivo* in chimpanzees. Pileri *et al.* show that preincubation of plasma (containing infections HCV) with sera (from chimpanzees vaccinated with E1 and E2 envelope proteins to cause protection) inhibited binding of HCV to its receptor (CD81) in an NOB assay (page 939, column 1, lines 58-63; see Figure 3D "beads-hEC2 + chimp No. 559 post immunization serum"). Sera from nonprotected chimpanzees was not inhibitory (page 939, column 1, lines 63-65; Figure 3D "beads-hEC2 + chimp No. 590 post immunization serum). Pileri *et al.* conclude "These results demonstrate that anti-E2 antibodies, which are capable of neutralizing HCV infection *in vivo*, can inhibit the binding of HCV to CD81 *in vitro*, supporting the idea that CD81-E2 interaction is relevant to infection" (page 939, column 2, lines 1-6).

The Pileri *et al.* reference demonstrates that NOB assay data correlates to *in vivo* neutralization activity. This correlation is directly applicable to the present invention, which correlates *in vitro* NOB activity to potential neutralizing effects *in vivo*. In addition, as stated in the specification at page 3, lines 15-22, "The finding that serum antibodies obtained from chimpanzees protected by vaccination were strongly positive in the NOB assay provides support for the relevance of the assay as a *measur*e of virus neutralization activity (Rosa *et al., supra*; Ishii *et al.,* 1998 *Hepatology* 28:1117-1120)." The Rosa *et al.* (Proc. Natl. Acad. Sci. USA (1996) 93:1761 (Exhibit C)) further state "we conclude that high titers of NOB antibodies are associated with protection from infection."

The NOB assay, being a *measure* of virus neutralization activity, can predict the *in vivo* neutralizing activity of antibodies. However, the results of the NOB assay are not absolute. As stated in the specification, "a strong neutralization of binding activity in and of itself does not *ensure* that an antibody will bind to intact HCV virions" (page 26, lines 4-5). It is possible that *not every* antibody identified by the NOB assay as having neutralization activity would correlate to neutralization activity *in vivo*. It is also possible that an antibody that lacks neutralization activity in an NOB assay might actually have neutralization activity *in vivo*. For example, Ishi et al. (Hepatology (1998) 28(4): Abstract (Exhibit D)) detect NOB activity in only 2 of 5 patients that recovered from acute hepatitis C infection. In these cases, the NOB assay can be used in combination with other assays to identify a pool of candidate antibodies that can be tested for viral neutralizing activity *in vivo*. This may include antibodies that did not have neutralization activity in the NOB assay.

Methods for testing viral neutralization activity *in vivo* are well known in the art. There are two standard *in vivo* assays by which to test the ability of an antibody to neutralize viral

activity. In one assay, antibodies are administered to chimpanzees that are chronically infected with the HCV virus (see, e.g., Ishi *et al.*, Hepatology (1998) 28(4): 1117-1120 or Rosa *et al.*, Proc. Natl. Acad. Sci. USA (1996) 93:1761 (Exhibits C andD)). Neutralization activity is determined by the ability of a virus to reduce the viral load in a chimpanzee. A second *in vivo* assay administers antibodies with potential neutralization activity to an uninfected chimpanzee before or just after administration of infection virus (Farci *et al*, Proc. Natl. Acad. Sci. USA, (1996) 93(24):15394-15399 (Exhibit E); Farci *et al.*, Proc. Natl. Acad. Sci. USA (1994) 91: 7792-7796 (Exhibit F); Krawczynski *et al.*, J. Infect. Dis. (1996) 173(4): 822-828 (Exhibit G) or Rosa *et al.*, Proc. Natl. Acad. Sci. USA (1996) 93:1761 (Exhibit C);). If the immunized chimpanzee is protected from infection, the antibody is a neutralizing antibody. The dose of antibody to administer is determined based on previous studies of polyclonal antibodies shown to prevent HCV infection in animals.

In summary, because the NOB assay is a proven predictor of neutralization activity *in vivo*, it can be used, as described in Example 5, to identify a pool of monoclonal antibodies that may be screened in further *in vivo* studies. However, because the results of the NOB assay are not absolute, some antibodies might need to be tested *in vivo*, regardless of their NOB performance. *In vivo* assays are well known in the art, as demonstrated above, and require no more than routine experimentation. In light of the above facts, withdrawal of this rejection is requested.

Claims 93 and 94 were rejected under 35 U.S.C. §112, first paragraph, on the assertion that the specification, while being enabling for the combination of the antibodies CBH-7 and CBH-4G, wherein the binding of one antibody to a conformational epitope results in increased

binding of the other antibody to a second conformational epitope, does not reasonably provide enablement for any and all combinations of antibodies wherein the combination results in increased binding of the antibodies to one or more conformational HCV E2 epitopes. The Examiner states that while the specification discloses selection of a variety of antibodies to HCV E2 conformational epitopes, only one very specific pair has the claimed properties. The Examiner argues that undue experimentation for one of skill in the art would be required to make a pair of antibodies with the required property. Applicant disagrees.

Claim 93 has been amended. Claim 93 now recites the combination of claim 92, wherein the combination shows increased total binding of the combined antibodies to the two or more different conformational epitopes of E2 protein of Hepatitis C virus than either antibody individually. Claims 103, 104, and 105 have been added. Claim 103 recites the combination of claim 92 comprising CBH-7 and CBH-5. Claim 104 recites the combination of claim 92 comprising CBH-7 and CBH-2. Claim 105 recites the combination of claim 93, wherein each antibody in the combination is directed to a different epitope. Claim 94 has been canceled.

The present specification shows that for a variety of antibody combinations that the presence of at least a second (or more) antibody to a binding reaction that binds a different epitope increases the total binding to E2 compared to the binding of either single antibody alone. For example, as shown in Figures 10-13, the presence of a second antibody, in addition to a first antibody, e.g., CHB-5 (Fig 11), CBH-2 (Fig. 12), or CBH-7 (Fig. 13), increases the total binding of the combined antibodies to the E2 protein compared to either antibody by itself. This applies generally to the combination of antibodies described herein and is not limited to CBH –7 and CBH-4G.

These teachings provide a person of ordinary skill in the art with tools sufficient to determine whether or not his or her particular combination of interest falls within a particular class of antibodies. If one of ordinary skill in the art wanted to test a specific antibody combination to see if the binding of each antibody in the combination had increased binding compared to the binding of the single antibody, one could simply carry out the experiments described in Figures 10-13 and at page 66, lines 3-7. In light of these facts and the amendments to claims 93 and 94, withdrawal of this rejection is requested.

Double Patenting

Claims 1, 3-23, 25-29, and 92-98 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 and 59 of co-pending Application No. 09/430,489.

Applicant respectfully refrains from responding to this provisional rejection until such time as it matures into an actual rejection.

Rejections Under 35 U.S.C. §102

Claims 1, 3, 15-17, 19, 21, 22, 25, 26, 29, 92, and 98 were rejected under 35 U.S.C. §102(a) as being anticipated by Da Silva Cardoso *et al.* (Journal of Virology 55:28-34, May 1998). The Examiner states that Da Silva Cardoso *et al.* disclose several human monoclonal antibodies to conformational epitopes on HCV E2, compositions comprising the antibodies that are not distinguished from the compositions of claim 29 and claim 98, and EBV-transformed human B cells that produce them, thus anticipating the subject matter of the cited claims. Applicant disagrees.

The monoclonal antibodies taught by Da Silva Cardoso *et al.* are not specific for HCV E2 conformational epitopes of *multiple genotypes* since 1a and 1b are only two different subtypes of one genotype rather than two different genotypes. The antibodies of the present claims are directed to a conformational epitope of a protein of Hepatitis C virus of more than one genotype. Without a teaching by Da Silva Cardoso *et al.* of an antibody specific for HCV E2 of *more than one genotype*, the reference cannot anticipate the claims of the present invention. In light of these facts, withdrawal of this rejection is requested.

Claims 1, 3, 13, 14, 22, 23, 25, 26, 28, 29, 92, and 98 were rejected under 35 U.S.C. §102(a) as being anticipated by Burioni *et al.* The Examiner indicates that these rejected claims enjoy the benefit of the filing date of 09/187,057 (11/5/98). The Examiner states that Burioni discloses human monoclonal recombinant antibody Fab fragments specific for HCV E2 conformational epitope (page 812, bottom column 1), compositions comprising the antibodies that are not distinguished from the compositions of claims 29 and 98, and the production of the Fab molecules in an *E. coli* system, thus anticipating the claimed subject matter. Applicant disagrees.

The teachings of Burioni do not anticipate the present invention now claimed in claims 1, 3, 13, 14, 22, 23, 25, 26, 28, 29, 92, and 98. Burioni does not teach monoclonal antibodies demonstrated to bind HCV E2 of *different genotypes* (*e.g.*, genotypes 1, 2, 3, 4, *etc*) (see also page 14, lines 4-6 and 14-15 of the specification). Rather, all of the antibodies disclosed in these references have been shown to bind only to E2 of subtype(s) of genotype 1 (e.g., subtypes 1a and/or 1b). No evidence is presented to show that the antibodies are cross-reactive with HCV E2

of *multiple genotypes*. The Examiner's assertion on page 10 of the Office Action that the antibodies of the claims are not distinguished from Burioni, is incorrect.

The Burioni *et al.* reference lacks any teaching of antibodies that bind to epitopes across multiple genotypes. A close reading of the paper shows that the antibody fragments (Fab) are derived from a patient infected with the HCV subtype 1b, and that the antibodies were evaluated for their reactivity against HCV E2 of the subtype 1a. For example, in the Discussion at page 814, the authors state that ". . . .our Fabs were selected by panning a library derived from a patient infected with an HCV of the 1b genotype against an E2 antigen from a virus of a 1 a genotype. . . " Without a teaching of antibodies specific for HCV E2 protein from multiple genotypes, this reference does not anticipate the presently claimed invention.

Claim 4 was rejected under 35 U.S.C. 102(b) as being anticipated by Burioni *et al.* cited above. The Examiner points to where Burioni discloses, "The inhibition constants shown in Fig. 3 are implying monomer Fab-antigen binding constant on the order of 10^7 to 10^8 mol/L^{-1}." The Examiner argues that considering the indefinite nature of claim 4 and the lack of explanation as to how the KD of the instant antibodies was actually determined, Burioni is deemed to anticipate the subject matter of claim 4. Applicant disagrees.

Claim 4 recites the antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-7} M. Claim 1, from which claim 4 depends, now recites, an antibody directed to a conformational epitope of a protein of Hepatitis C virus of more than one genotype. Because claim 4 includes the limitations of claim 1 and the Burioni *et al.* reference lacks any teachings of antibodies that cross-react with conformational epitopes of HCV

E2 of more than one genotype, Burioni cannot anticipate claim 4. Given these differences, the K_D is irrelevant. Withdrawal of this rejection is requested.

Claims 1, 3, 4, 5, 14, 15, 22, 23, 25, 26, 28, 29, 92, and 98 were rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/40167, Persson *et al.* published 10/ 30/97. The Examiner states that Persson *et al.* disclose recombinant human monoclonal antibodies specific for conformational HCV E2 epitopes that have Kds of as little as 6 nM, i.e., less than 10^{-8} M (see, e.g., Table III). Applicant disagrees.

Independent claim 1 (and dependent claims 4, 5, 15, 22, 23, 25, 26, 28, 29) recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus of more than one genotype. Independent claim 3 (and dependent claims 14, 25, 26) recites an antibody directed to a conformational epitope of E2 protein of Hepatitis C virus of more than one genotype. Independent claim 92 (and dependent claim 98) recites a combination of two or more antibodies each of which is directed to one or more conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype.

The antibodies of the present invention were obtained by a hybridoma. As described in the specification, the hybridomas were derived from B cells isolated from an HCV infected individual. One advantage of the antibodies produced by a hybidoma is that they are generated against HCV epitopes that result from an *in vivo* infection. Thus, antibodies provided by the hybridomas are more likely to bind epitopes presented by the HCV virus *in vivo.*

In contrast, the monoclonal antibodies described by Persson *et al.* were obtained using a combinatorial antibody library constructed from bone marrow lymphocytes from an HCV (genotype 2b) infected donor (see Examples 1 and 2 and page 20). The Persson *et al.* antibodies

result from random recombination and assembly of Fab and Fc fragments. Furthermore, the antibodies of Persson *et al.* were screened *in vitro* against recombinant antigens. It is probably that recombinant HCV antigens will not present conformational epitopes in their native state. Consequently, a combinatorial library generated by random recombination events and screened against synthetic antigens *in vitro*, such as the one generated by Persson *et al.*, is likely to produce antibodies to different antigen targets than the *in vivo* targets of an HCV infected individual. The recombinant antibodies identified are therefore likely to have different epitope binding profiles than the antibodies screened against native HCV virion antigens as part of the natural immune response of the host to HCV infection. Such antibodies cannot be identical to the antibodies of the claims.

In light of the above, Persson *et al.* do not anticipate claim 4 and this rejection should be withdrawn.

Claims 1, 15-19, 21, 22, 25, 26, 28, and 29 were rejected under 35 U.S.C. 102(b) as being anticipated by Mondelli *et al.* (Journal of Virology 68(8): 4829-4836, 1994). The Examiner states that Mondelli *et al.* disclose a human monoclonal antibody to a conformational epitope on HCV NS3, compositions comprising the antibody that are not distinguished from the composition of claim 29, and the EBV-transformed human B cell line that produces it, thus anticipating the subject matter of the cited claims. Applicant disagrees.

Claim 1 now recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype.

The human monoclonal antibodies described by Mondelli *et al.* bind to the nonstructural protein NS3 of HCV. The antibodies of claim 1 (and all claims that depend from claim 1) are

directed to the HCV E2 protein. Thus, since the antibodies are directed to completely different proteins on HCV, Mondelli *et al.* clearly cannot anticipate claims 1, 15-19, 21, 22, 25, 26, 28, and 29. Furthermore, the antigens used to screen for these antibodies are not likely to maintain native structures. Withdrawal of this rejection is requested.

Claims 1, 3, 15, 18, 19, 20, 25, 28, and 29 were rejected under 35 U.S.C. 102(b) as being anticipated by Deleersnyder *et al.* (Journal of Virology 71(1):697-704, January 1997). The Examiner states that Deleersnyder *et al.* disclose a murine monoclonal antibody to a conformational epitope of HCV E2, compositions comprising the antibody that are not distinguished from the composition of claim 29, and a hybridoma cell line that produces it, thus anticipating the subject matter of the cited claims.

Claim 1 now recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype. Claim 3 now recites an antibody directed to a conformational epitope of E2 protein of Hepatitis C virus of more than one genotype.

Like Burioni, Deleersnyder *et al.* do not provide any teachings of monoclonal antibodies to the Hepatitis C virus E2 protein that recognize E2 conformational epitopes from more than one genotype of HCV. Indeed the only genotype of HCV mentioned by Deleersnyder *et al.* is HCV-H subtype 1a (see page 698, column 1, last paragraph). Since Deleersnyder *et al.* do not teach of any other genotype, other than subtype 1, to which the monoclonal antibodies bind, Deleersnyder *et al.* cannot anticipate the invention claimed in claims 1, 3, 15, 18, 19, 20, 25, 28, and 29. Withdrawal of this rejection is requested.

Claims 1, 3, 15-19, 21, 22, 25, 26, 28, 29, 92, and 98 were rejected under 35 U.S.C. 102(b) as being anticipated by Habersetzer *et al.* Hepatology 24(4), Pt. 2, 381A, Abstract 1020, 1996. The Examiner states that Habersetzer *et al.* disclose several human monoclonal antibodies to conformational epitopes on HCVE2, compositions comprising the antibodies that are not distinguished from the compositions of claim 29 and claim 98, and EBV-transformed human B cells that produce them, thus anticipating the subject matter of the claimed invention. Applicant disagrees.

Independent claim 1 (and dependent claims 15, 19-22, 25, 26, 28, 29) recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus of more than one genotype. Independent claim 3 (and dependent claims 25, 26) recites an antibody directed to a conformational epitope of E2 protein of Hepatitis C virus of more than one genotype. Independent claim 92 (and dependent claim 98) recites a combination of two or more antibodies each of which is directed to one or more conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype.

It is well known by those skilled in the art that in the HCV nomenclature, the numbers, e.g., "1," represents the HCV genotype and the letters, "a" or "b," represents the HCV subtype. Those skilled in the art would further recognize that it is implicit that the statement "HCV genotype 1a" represents HCV genotype 1, subtype a.

Proof of the validity of this statement can be found in *Hepatitis News Stories:* "Hepatitis C Virus (HCV) Genotype and Subtype Transmission Have Distinct Patterns" by Brian Bolye, MD found on the world wide web at http://www.hivandhepatitis.com/hep_c/news/092401d.html (Exhibit H). The third paragraph of this article states:

> "HCV *genotypes 1, 2, and 3* were present in 95%, 1%, and 3%, respectively, of the patients and 1% could not be *typed*. Of the genotype 1 patients, 24% were *subtype 1a* and 76% were *subtype 1b*. "

The article continues in the fourth paragraph:

> "The individuals infected with *HCV 1a* and *1b* with an IDU risk factor were significantly younger than non-IDU individuals infected with those *subtypes*, and patients infected with *subtype* 1b were significantly older than those infected with 1a."

And in paragraph five, the authors conclude:

> '[t]hese observations suggest a distinct pattern of HCV *genotype* and *subtype* transmission in Prague populations. These observations suggest that *subtype* 1b may have been present in Prague for a longer time than *subtype* 1a.'"

This article clearly demonstrates that the genotypes of HCV are denoted by numeral, e.g., 1, 2, 3. The subtypes are referred to using the letter designations "a" and "b." In addition, the Boyle article clearly demonstrates the implicit use of the term "HCV 1a" to denote HCV of genotype "1" subtype "a." Using the Boyle reference as a guide the antibodies disclosed by Habersetzer *et al.* (Hepatology, 1996), which are capable of recognizing HCV E2 genotypes 1a and 1b, are *not* cross reactive against multiple genotypes, but are cross reactive against multiple subtypes (subtypes a and b) within a single genotype (genotype 1).

In light of the above, Applicant submits that the present invention is not anticipated by Habersetzer *et al.* because the monoclonal antibodies described by Habersetzer *et al.* do not bind the epitope in envelope proteins from more than one HCV genotype. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §103

Claims 8-13 were rejected under 35 U.S.C. §102(a) as being anticipated by, or alternatively under 35 U.S.C. §103(a) as being obvious over either one of Da Silva Cardoso *et al.* or Burioni *et al.* as cited above. The Examiner states that the antibodies of Da Silva Cardoso and of Burioni *et al.* reasonably appear to be the same as, or only slightly different from the claimed antibodies in terms of their binding specificities since they were obtained from HCV infected individuals as were Applicant's, they were selected for binding specificity in the same manner as were Applicant's, they bind to conformational epitopes on the HCV E2 protein as do Applicant's, and they give the same or similar results in neutralization of binding assays as do Applicant's antibodies. The Examiner concludes that in the absence of factual evidence to the contrary, they reasonably appear to be the same as or only slightly different from the antibodies of claims 8-13. Applicant disagrees.

Claim 8 recites an antibody directed to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype. Claim 9 recites an antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype. Claim 10 recites an antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b and exhibits minimal cross-competition with the antibodies of claim 8, wherein the antibody binds specifically to the E2 protein of Hepatitis C virus of more than one genotype. Claim 11 recites an antibody directed to an epitope within amino acids 644 through 661 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of

more than one genotype. Claim 12 recites an antibody directed to the epitope recognized by CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -17. Claim 13 recites an antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -17 for binding to its epitope.

Neither Da Silva Cardoso *et al.* or Burioni teach monoclonal antibodies demonstrated to bind HCV E2 of different genotypes (*e.g.*, 1, 2, 3, 4, *etc*). Rather, all the antibodies disclosed in these references have been shown to bind only to E2 of different subtype(s) of genotype 1. No evidence is presented in any of the papers to show that the antibodies are cross-reactive with HCV E2 of *multiple genotypes*. In addition, Da Silva Cardoso et al. and Burioni are both completely lacking in any teachings of a specific binding region of the E2 protein of HCV 1b, as is presently claimed.

Da Silva Cardoso *et al.* do not teach monoclonal antibodies that are specific for HCV E2 conformational epitopes of *multiple genotypes* since 1a and 1b are only two different subtypes of one genotype rather than two different genotypes. The antibodies of the present claims are directed to a conformational epitope of a protein of Hepatitis C virus of more than one genotype. In addition, Da Silva Cardoso merely identified antibodies that bound to the envelope protein E2 of HCV genotypes 1a and 1b (see Abstract and Table 1). They did not map specific binding epitopes within HCV 1b. Without a teaching or suggestion by Da Silva Cardoso *et al.* of an antibody specific for HCV E2 of *more than one genotype*, and without teaching specific HCV 1b epitopes, the Da Silva Cardoso reference cannot anticipate nor render obvious the claims of the present invention. In light of these facts, withdrawal of this aspect of the rejection is requested.

Like Da Silva Cardoso, Burioni et al. lack any teachings of specific regions within HCV 1b E2 to which antibodies bind. Burioni et al. merely test the ability of HCV E2 specific

antibodies to neutralize the binding of HCV E2 to target cells (see Table 1 and Figure 2). On this basis alone, claims 8-13 are novel and non-obvious over Burioni.

However, to address this rejection thoroughly, the Burioni *et al.* reference does not disclose the selection of human monoclonal recombinant Fab fragments specific for HCV E2 conformational epitopes that are cross-genotype reactive. As pointed out above, Burioni *et al.* demonstrate that the antibody fragments (Fab) are derived from a patient infected with the HCV subtype 1b, and that the antibodies were evaluated for their reactivity against HCV E2 of the subtype 1a. No genotype other than genotype 1 is described in the paper. Therefore, there is no indication that the antibodies are specific for HCV E2 protein from multiple genotypes. Moreover, these antibodies are generated from random recombination of Ig genes and selected using recombinant HCV proteins. Because of the difficulties in expressing native recombinant HCV proteins, these antibodies are likely to bind different epitopes than those of the present claims.

The authors of this reference state, starting on page 813, second column, and continuing on the next page:

> "Finally, even if only indirectly, our data suggest that some of the Fabs could be cross-reactive among different *strains*. Obviously, before drawing any conclusion, more accurate experimentation must be performed on primary isolates to more accurately evaluate the Fabs' neutralizing activity and cross-reactivity. Because our Fabs were selected by panning a library derived from a patient infected with an HCV of the 1b genotype against an E2 antigen from a virus of 1a genotype, ..."

In this passage, Burioni only mention the possibility of the antibody fragments being cross-reactive with multiple *strains* not *multiple genotypes*. Burioni et al. even acknowledge that additional experimentation would be required to determine if Fabs are cross-reactive against

different *strains*. Without any teaching or suggestion of antibodies specific for HCV E2 protein from multiple genotypes, this reference cannot render the presently claimed invention obvious.

Claims 8-13 were also rejected under 35 U.S.C. §102(a) as being anticipated by, or alternatively under 35 U.S.C. §103(a) as being obvious over any one of Persson *et al.*, Deleersnyder *et al.*, or Habersetzer *et al.* The Examiner states that the antibodies of Persson *et al.*, Deleersnyder *et al.*, or Habersetzer *et al.*, reasonably appear to be the same as, or only slightly different from, the claimed antibodies since they were obtained from HCV infected individuals, they were selected in the same manner, they bind to conformational epitopes on the HCV E2 protein, and they give the same or similar results in neutralization of binding assays. The Examiner concludes that in the absence of factual evidence to the contrary, they reasonably appear to be the same as or only slightly different from the antibodies of claims 8-13. Applicant disagrees.

Claim 8 recites an antibody directed to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype. Claim 9 recites an antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype. Claim 10 recites an antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b and exhibits minimal cross-competition with the antibodies of claim 8, wherein the antibody binds specifically to the E2 protein of Hepatitis C virus of more than one genotype. Claim 11 recites an antibody directed to an epitope within amino acids 644 through 661 of E2 protein of Hepatitis

C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype. Claim 12 recites an antibody directed to the epitope recognized by CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -17. Claim 13 recites an antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -17 for binding to its epitope.

Beginning with Persson *et al.*, this reference does not anticipate the present invention on the following bases. Because the antibodies of Persson *et al.* are generated by an *in vitro* recombination method, they are likely to be completely different in structure and epitope-recognition ability than antibodies produced by hybridomas from cells *in vivo*, such as those of the present invention, and thus do not anticipate the antibodies of the present claims. For the following reasons, Persson *et al.* do not make the present claims 8-13 obvious.

The Cited References Do Not Establish a Prima Facie Case of Obviousness

Applicant submits that a *prima facie* case of obviousness under § 103 has not been established. According to the Manual of Patent Examining Procedure ("MPEP"),

[t]he examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or reference when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art and not based on applicant's disclosure. MPEP § 2142, citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (fed. Cir. 1991). (Emphasis added)

Here, this initial burden has not been met. Applicant asserts that the prior art provides neither the suggestion nor the motivation to modify the reference, nor does the reference teach or suggest all of the limitations of the claimed invention. Moreover, the cited references provide no reasonable expectation that such a combination would have led to success.

The Cited Art

Looking to Persson *et al.*, this reference teaches producing monoclonal antibodies by generating a combinatorial antibody library constructed from a nonimmunized, HCV-infected donor (see page 20, lines 5-9). More specifically, the monoclonal antibodies are obtained from combinatorial libraries expressing Fab molecules on the surface of filamentous DNA bacteriophage using antigen selection techniques (see page 20, lines 9-13). In contrast, the antibodies of claims 8-13 are produced by a hybridoma, which was cloned by the following process:

> (1) Individuals with evidence of exposure to HCV were identified; (2) antigen specific B-cells from their peripheral blood were expanded and activated *in vitro*; (3) these cells were immortalized by electrofusion with a suitable mouse-human heteromyeloma; (4) relevant human antibody secreting hybridomas were identified; and (5) the relevant hybridomas were stabilized by cloning (page 24, lines 5-10).

The Examiner's argument makes it sound as if the prior art references disclose the claimed antibodies by stating that the antibodies "appear to be the same as or only slightly different from the claimed antibodies since they were obtained from HCV infected individuals" etc. (see page 13 of the Office Action). However, the antibodies of Persson *et al.*, because they are produced recombinantly and screened against synthetic antigens *in vitro*, are unlikely to even remotely resemble antibodies actually produced by hybridomas, which represent those produced *in vivo* in

response to HCV infection. Indeed, entirely unique antibodies with antigen specificities that do not even resemble the specificities of the antibodies expressed *in vivo* are expected to be produced using recombination.

The Cited Art does not Teach or Suggest All of the Limitations of the Claimed Invention

There is no teaching or suggestion in Persson *et al.* of generating human monoclonal antibodies using a hybridoma. Nor is there any basis from which to assert that Persson *et al.* disclose human monoclonal antibodies with the same binding specificities as the antibodies listen in claims 8-13, regardless of their source. Therefore, Persson *et al.* do not teach or suggest all of the limitations of the claimed invention.

The Cited Art Provides No Reasonable Expectation of Success

The case law is clear that, for an invention to be obvious, there must also be some suggestion of a reasonable expectation of success. This suggestion must be found in the prior art, and not in the Applicant's specification. As the Federal Circuit held *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2D 1438 (Fed. Cir. 1991),

> a proper analysis under § 103 requires *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. (Emphasis added; citations omitted)

As pointed out above, Persson *et al.* is completely lacking of any teaching or suggestion of antibodies produced by hybridomas. There is clearly no reasonable expectation that the monoclonal antibodies of Persson *et al.* would be directed to specific conformational epitopes on

HCV 1b that are cross-react with HCV E2 epitopes of different genotypes. Only the present invention demonstrates the success of producing human monoclonal antibodies to conformational epitopes on HCV, which cross-react with different genotypes. And as the courts have ruled, the Applicant's specification cannot provide this suggestion.

Furthermore, as noted above, the antibodies obtained recombinantly would almost certainly have different specificities than the antibodies one would obtain from a hybridoma. Recombinant antibodies are screened *in vitro* against synthetic antigens, while hybridomas produce antibodies to infectious virion particles *in vivo*. Moreover, the structure of the recombinant antibodies is most likely to be completely different from the hybridoma antibodies.

The reference by Persson *et al.*, while providing recombinant human monoclonal antibodies, does not provide the antibodies of claims 8-13. In light of the above discussion, Applicant submits that a *prima facie* case of obviousness has not been established for the antibodies of claims 8-13, and on this basis alone, the rejection under § 103 should be withdrawn.

Turning to Deleersnyder *et al.*, this reference lacks any teachings of specific regions of HCV E2 1b that are bound by monoclonal antibodies. In addition, this reference lacks any teaching of monoclonal antibodies that recognize E2 conformational epitopes from more than one genotype of HCV. Indeed the only genotype of HCV mentioned by Deleersnyder *et al.* is HCV-H subtype 1a (see page 698, column 1, last paragraph). Since Deleersnyder *et al.* do not disclose specific HCV 1b E2 epitopes and do not teach of any other genotype, other than subtype 1, to which the monoclonal antibodies bind, Deleersnyder *et al.* cannot anticipate nor render obvious the invention claimed in claims 8-13. Withdrawal of this rejection is requested.

Like Deleersnyder *et al.*, Habersetzer *et al.* (Hepatology, Supplement, Vol. 24, no. 4, part 2, October 1996, Abstract No. 1020, P. 381A) discloses human monoclonal antibodies isolated from a HCV 1b infected patient that react to an undefined, conserved, conformational HCV 1a epitope. Recognition of no other genotype is taught of suggested in the reference. As discussed herein, 1a and 1b are subgentypes of genotype 1. There is no cross-genotype recognition or binding demonstrated by the antibodies and no specific epitopes are described by Habersetzer (Hepatology).

Claims 8-13 recite human monoclonal antibodies that binds to epitopes in envelope proteins from *more than one* HCV genotype. Without testing against HCV E2 protein derived from multiple genotypes, there is no evidence to say that the antibodies are specific for HCV E2 protein of multiple genotypes. Without evidence that the monoclonal antibodies of Habersetzer *et al.* recognize HCV E2 of multiple genotypes, the Habersetzer reference cannot anticipate nor render the presently claimed invention obvious.

Claims 5-7 were rejected under 35 U.S.C. §103(a) as being obvious over Burioni et al. The Examiner states that Burioni discloses human monoclonal recombinant Fab fragments specific for HCV E2 conformational epitopes, discloses monomer Fab-antigen binding constants on the order of 10^7 to 10^8 mol/L^{-1}, and suggests selecting high-affinity human monoclonal antibodies (see, e.g., first sentence of paragraph bridging pages 810-811). The Examiner concludes that it would have been obvious to one of ordinary skill in the art to select high-affinity monoclonal antibodies to conformational HCV epitopes as recited in claims 5-7 because Burioni teaches the selection of high-affinity human monoclonal antibodies from random combinatorial libraries.

Claim 5 recites the antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-8} M. Claim 6 recites the antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-9} M. Claim 7 recites the antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-10} M. Independent claim 1 recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype.

The Burioni *et al.* reference does not disclose the selection of human monoclonal recombinant Fab fragments specific for HCV E2 conformational epitopes that are cross-genotype reactive. As pointed out above, Burioni *et al.* demonstrates that the antibody fragments (Fab) are derived from a patient infected with the HCV subtype 1b, and that the antibodies were evaluated for their reactivity against HCV E2 of the subtype 1a. No genotype other than genotype 1 is described in the paper. Therefore, there is no indication that the antibodies are specific for HCV E2 protein from multiple genotypes.

Burioni *et al.* acknowledge that additional experimentation would be required to determine if the Fabs are cross-reactive against different *strains* (p. 813). However, there is no mention in Burioni et al. of the possibility of the antibody fragments being cross-reactive with *multiple genotypes*. Due to their dependency on claim 1, claims 5-7 are directed to antibodies that bind to a conformational E2 protein of HCV from *more than one genotype*, which have dissociation constants for its epitope of less than 10^{-8} (claim 5), less than 10^{-9} (claim 6), or less than 10^{-10} (claim 7). Without a teaching or suggestion of antibodies specific for HCV E2 proteins of multiple genotypes that have these dissociation constants, this reference does not anticipate the present invention; nor can it render the presently claimed invention obvious.

Applicant thanks the Examiner for acknowledging that claims 27, 30-32, 66, 67, 70, 99, 100, 93, and 94 are free of prior art of record.

The Examiner also states that claims 95-97 would be allowable if the claims were rewritten to be limited to the specifically recited monoclonal antibodies, the biological deposit conditions were met, and the obviousness double patenting issue were to be settled. Applicant submits that the Amendment and Remarks of the present Response has put these claims in condition for allowance.

Applicant thanks the Examiner for careful consideration of this case. Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

Brenda Herschbach Jarrell, PhD.
Reg. No. 39,223

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
Tel: (617) 248-5000
Dated: April 22, 2002

APPENDIX A
VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Specification:

The specification has been amended as follows.

The paragraph beginning at page 6, line 14, has been replaced with the following rewritten paragraph.

One aspect of the present invention provides monoclonal antibodies, including human monoclonal antibodies, which bind to the dominant HCV types in major geographical areas. The dissociation constants for these antibodies for their epitopes ranges from less than 10^{-7}M to less than 10^{-8}M to less than 10^{-9}M. Specifically, a family of monoclonal antibodies binding to conformationally conserved epitopes of the HCV E2 protein is provided. Among the family are antibodies that bind to the dominant genotypes found in the United States, so as to be substantially pan-monoclonal antibodies in being able to bind to almost all cases of HCV infection, which have been diagnosed in the United States, as well as at least a substantial proportion of the cases in other geographic locales. The monoclonal antibodies find use in a variety of diagnostic assays. In addition, conformationally conserved expression of recombinant type 1 and type 2 HCV E2 proteins and fragments thereof are provided for use in assays, screening drugs, vaccines, diagnostic assays, and for other purposes. The inventive antibodies find use in passive immunotherapy strategies for reducing viral load of infected individuals and interfering with the infection of target cells. Antibodies recognizing conformationally dependent epitopes can also be used to provide a template for the rational design of peptide and conformationally-defined epitope mimetics (*e.g.*, organic compounds, organometallic compounds, inorganic compounds, small molecules).

The following paragraph has been inserted at page 24, line 5.

Mouse/human heteromyeloma cell lines expressing monoclonal antibody CBH-4B and CBH-4G were deposited on June 18, 2002 with the American Type Culture Collection (ATCC) (10801 University Blvd., Manassas, VA 20110-2209) and assigned ATCC numbers PTA-4466 and PTA-4468, respectively. Also included in this deposit were other mouse/human heteromyeloma cell lines expressing antibodies CBH-2 (PTA-4465), CBH-4B (PTA-4466), CBH-4D (PTA-4467), CBH-4G (PTA-4468), CBH-5 (PTA-4469), CBH-7 (PTA 4470), CBH-8 (PTA-4471), CBH-11 (PTA-4472) and CBH-17 (PTA-4473), described herein below.

In the Claims

Claims 1, 3, 4-13, 25-27, 30, 32, and 92-100 have been amended to read as indicated below.

Claims 66 and 94 has been canceled.

Claims 101-105 have been added.

1. (Amended) An antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype.

3. (Deleted) An antibody directed to a conformational epitope of E2 protein of Hepatitis C virus.

5. (Amended) The antibody of claim 1 wherein the [binding] dissociation constant (K_D) of the antibody for its epitope is less than 10^{-8} M.

6. (Amended) The antibody of claim 1 wherein the [binding] dissociation constant (K_D) of the antibody for its epitope is less than 10^{-9} M.

7. (Amended) The antibody of claim 1 wherein the [binding] dissociation constant (K_D) of the antibody for its epitope is less than 10^{-10} M.

8. (Amended) An antibody directed to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

9. (Amended) An antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

10. (Amended) An antibody directed to a [conformation] conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b and exhibits minimal cross-competition with the antibodies of claim 8, wherein the antibody binds specifically to the E2 protein of Hepatitis C virus of more than one genotype.

11. (Amended) An antibody directed to an epitope within amino acids 644 through 661 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

12. (Amended) An antibody directed to the epitope recognized by CBH-2, -4D, -4B, -4G, -5, -7, -8C, [-8E, -9], or –11[, or –17].

13. (Amended) An antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, [-8E, -9,] or –11[, or –17] for binding to its epitope.

14. (Amended) The antibody of claim [3] 1 wherein the antibody inhibits binding of HCV E2 to CD81.

25. (Amended) The antibody of claim 1, [2, 3,] 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a monoclonal antibody.

26. (Amended) The antibody of claim 1, [2, 3,] 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a human antibody.

27. (Amended) The antibody of claim 1, [2, 3,] 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a humanized antibody.

30. (Amended) A method of treating or preventing HCV infection in a patient [a patient infected with HCV], the method comprising steps of:

providing a patient infected with HCV or susceptible to HCV infection; and

administering to the patient the antibody of claim 1.

32. (Amended) The method of claim 30 or 31 wherein the step of administering the antibody comprises administering more than one different antibody, wherein at least one of the antibodies is directed to a conformational epitope of a protein of Hepatitis C virus.

66. (Canceled) A method of classifying patients infected with HCV, the method comprising steps of:

providing serum from a patient infected with HCV;

measuring inhibition by the patient's serum of binding of an anti-HCV monoclonal antibody to its epitope; and

identifying patient as candidate for administration of a treatment.

70. (Amended) The method of claim [66] 67, wherein the step of administering comprises administering an antibody directed to the epitope that is bound by an anti-HCV monoclonal antibody, the binding of which is not inhibited by the patient's serum.

92. (Amended) A combination of two or more antibodies directed to [one] two or more different conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype.

93. (Amended) The combination [of two or more antibodies] of claim [75] 92, wherein the combination [results in] shows increased total binding of the combined antibodies to [one or more different conformational epitopes of] E2 protein of Hepatitis C virus compared to either antibody individually.

94. (Canceled) The combination of two or more antibodies of claim 76, wherein the increased binding of two or more antibodies to the one or more conformational epitopes of E2 protein of Hepatitis C virus is greater than 100% relative to the binding of a single antibody.

95. (Amended) The combination [of two or more antibodies] of claim [75] 92 comprising CBH-7 and CBH-4G.

96. (Amended) The combination [of two or more antibodies] of claim [75] 92 comprising CBH-7 and CBH-4D.

97. (Amended) The combination [of two or more antibodies] of claim [75] 92 comprising CBH-7 and CBH-17.

98. (Amended) A pharmaceutical composition comprising the [antibodies] combination of claim [75, 76, 77, 78, 79, or 80] 92, 93, 94, 95, 96, or 97 and a pharmaceutically acceptable excipient.

99. (Amended) A method of treating or preventing HCV infection in a patient [a patient infected with HCV], the method comprising steps of:

providing a patient infected with HCV or susceptible to HCV infection; and

administering to the patient the [antibodies] combination of claim [75, 76, 77, 78, 79, or 80] 92, 93, 94, 95, 96, or 97.

100. (Amended) A method of treating a patient that has been exposed to HCV, the method comprising steps of:

providing a patient that has been exposed to HCV; and

administering to the patient the antibody of claim [75, 76, 77, 78, 79, or 80] 92, 93, 94, 95, 96, or 97.

Claims 101-105 have been added as follows.

--101. (New) A combination of two or more antibodies, wherein at least one antibody is directed to a conformational epitope of E2 protein of Hepatits C virus of more than one genotype.

102. (New) The combination of claim 101, wherein the combination shows increased binding to the epitopes of E2 protein of Hepatitis C virus than either antibody individually.

103. (New) The combination of claim 92 comprising CBH-7 and CBH-5.

104. (New) The combination of claim 92 comprising CBH-7 and CBH-2.

105. (New) The combination of claim 93, wherein each antibody in the combination is directed to a different epitope.--

Appendix B
Claims as Pending After Entrance of the Present Amendment

1. An antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype.

4. The antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-7} M.

5. The antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-8} M.

6. The antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-9} M.

7. The antibody of claim 1 wherein the dissociation constant (K_D) of the antibody for its epitope is less than 10^{-10} M.

8. An antibody directed to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

9. An antibody directed to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

10. An antibody directed to an epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b and exhibits minimal cross-competition with the antibodies of claim 8, wherein the antibody binds specifically to the E2 protein of Hepatitis C virus of more than one genotype.

11. An antibody directed to an epitope within amino acids 644 through 661 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype.

12. An antibody directed to the epitope recognized by CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -11.

13. An antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -11 for binding to its epitope.

14. The antibody of claim 1 wherein the antibody inhibits binding of HCV E2 to CD81.

15. A cell line expressing the antibody of claim 1.

16. The cell line of claim 15 wherein the cell line is a B cell line.

17. The cell line of claim 15 wherein the cell line is a human cell line.

18. The cell line of claim 15 wherein the cell line is a mammalian cell line.

19. The cell line of claim 15 wherein the cell line is a eukaryotic cell line.

20. The cell line of claim 15 wherein the cell line is a hybridoma.

21. The cell line of claim 15 wherein the cell line has been transformed with Epstein-Barr virus (EBV).

22. The cell line of claim 15 wherein the cell line has been infected with a virus.

23. The cell line of claim 15 wherein the cell line has been infected with phage.

25. The antibody of claim 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a monoclonal antibody.

26. The antibody of claim 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a human antibody.

27. The antibody of claim 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 wherein the antibody is a humanized antibody.

28. The antibody of claim 1 wherein the antibody is a mammalian antibody.

29. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable excipient.

30. A method of treating or preventing HCV infection in a patient, the method comprising steps of:

providing a patient infected with HCV or susceptible to HCV infection; and

administering to the patient the antibody of claim 1.

31. A method of treating a patient exposed to HCV, the method comprising steps of:

providing a patient exposed to HCV; and

administering to the patient the antibody of claim 1.

32. The method of claim 30 or 31 wherein the step of administering the antibody comprises administering more than one different antibody, wherein at least one of the antibodies is directed to a conformational epitope of a protein of Hepatitis C virus.

67. The method of claim 66, the method comprising additional step of:

administering to the patient an antibody.

70. The method of claim 67, wherein the step of administering comprises administering an antibody directed to the epitope that is bound by an anti-HCV monoclonal antibody, the binding of which is not inhibited by the patient's serum.

92. A combination of two or more antibodies directed to two or more different conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype.

93. The combination of claim 92, wherein the combination shows increased total binding of the combined antibodies to E2 protein of Hepatitis C virus compared to either antibody individually.

95. The combination of claim 92 comprising CBH-7 and CBH-4G.

96. The combination of claim 92 comprising CBH-7 and CBH-4D.

97. The combination of claim 92 comprising CBH-7 and CBH-17.

98. A pharmaceutical composition comprising the combination of claim 92, 93, 94, 95, 96, or 97 and a pharmaceutically acceptable excipient.

99. A method of treating or preventing HCV infection in a patient, the method comprising steps of:

providing a patient infected with HCV or susceptible to HCV infection; and

administering to the patient the combination of claim 92, 93, 94, 95, 96, or 97.

100. A method of treating a patient that has been exposed to HCV, the method comprising steps of:

providing a patient that has been exposed to HCV; and

administering to the patient the antibody of claim 92, 93, 94, 95, 96, or 97.

101. A combination of two or more antibodies, wherein at least one antibody is directed to a conformational epitope of E2 protein of Hepatits C virus of more than one genotype.

102. The combination of claim 101, wherein the combination shows increased binding to the epitopes of E2 protein of Hepatitis C virus than either antibody individually.

103. The combination of claim 92 comprising CBH-7 and CBH-5.

104. The combination of claim 92 comprising CBH-7 and CBH-2.

105. The combination of claim 93, wherein each antibody in the combination is directed to a different epitope.